Syndromes, Disorders and Maternal Risk Factors Associated with Neural Tube Defects (II)

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SUMMARY

Fetuses with neural tube defects (NTDs) may be associated with syndromes, disorders, and maternal risk factors. This article provides a comprehensive review of syndromes, disorders, and maternal risk factors associated with NTDs, such as Currarino syndrome, sacral defect with anterior meningocele, Jarcho-Levin syndrome (spondylocostal dysostosis), lateral meningocele syndrome, neurofibromatosis type I, Marfan syndrome, and hyperthermia. The recurrence risk and the preventive effect of maternal folic acid intake in NTDs associated with syndromes, disorders, and maternal risk factors may be different from those of non-syndromic multifactorial NTDs. Perinatal identification of NTDs should alert one to the syndromes, disorders, and maternal risk factors associated with NTDs, and prompt a thorough etiologic investigation and genetic counseling. [*Taiwan J Obstet Gynecol* 2008;47(1):10–17]

Key Words: congenital malformations, disorder, maternal risk factors, neural tube defects, syndromes

Introduction

Neural tube defects (NTDs) have an incidence of 1–2 per 1,000 births and are considered to be a heterogeneous condition resulting from failure of normal neural tube closure between the third and fourth week of embryonic development. The three common types of NTDs are anencephaly, spina bifida, and encephalocele. The uncommon types of NTDs include amniotic band syndrome, limb–body wall complex, cloacal exstrophy or OEIS complex, and other types of spinal abnormalities. The incidence of NTDs varies with race, geographic variation, socioeconomic classes, nutritional status, and multiple predisposing factors such as single gene disorders, chromosomal abnormalities, teratogens, maternal diabetes, family history of NTDs, thermolabile mutation in the *MTHFR* gene, and others [1]. There is considerable evidence that genetics and environmental factors contribute to the etiology of NTDs. Fetuses with NTDs may be associated with syndromes, disorders, and maternal risk factors.

Currarino Syndrome

Yates et al [2] first recognized the autosomal dominant inheritance in Currarino syndrome. Currarino syndrome (OMIM 176450) or Currarino triad is characterized by the triad of anorectal, sacral and presacral anomalies: (1) a partial sacral agenesis with intact first sacral vertebra; (2) a presacral mass such as anterior meningocele, neuroenteric cyst, dermoid or epidermoid cyst, lipoma, hamartoma, unclassified tumor, presacral

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teratoma or a combination of these; and (3) anorectal malformations such as anorectal stenosis, imperforate anus and anorectal sinus [3,4]. Other associated malformations include duplex ureters, horseshoe or duplex kidneys, vesicoureteric reflux, secondary hydronephrosis, a bicornuate uterus, rectovaginal fistula, a septate vagina, spinal cord tethering, and neuroenteric cysts [4]. In a study of 205 patients with Currarino syndrome, Lynch et al [4] found asymptomatic subjects in 33% of the cases, anterior meningocele in 50% of the cases, and a presacral mass (teratoma, lipoma or cyst) in 42% of the cases. Weinberg [5] suggested that the presacral masses described as teratomas in Currarino syndrome are actually hamartomas due to the absence of any well-documented example of malignant germ cell tumor associated with Currarino syndrome. The risk of malignant transformation in the presacral teratomas of Currarino syndrome is about 1%, which is much lower than the risk of malignant transformation in sacrococcygeal teratomas [4]. Ross et al [6] demonstrated the homeobox gene of *HLXB9* (OMIM 142994) at 7q36 as the major locus for Currarino syndrome. Hagan et al [7] identified mutations in the coding sequence of *HLXB9* in 95% (20/21) of cases of familial Currarino syndrome and in approximately 30% (2/7) of patients with sporadic Currarino syndrome. Remarkable phenotypic variability and asymptomatic status in half of the carriers have been observed in the family members with mutations of the *HLXB9* gene and Currarino syndrome [8,9]. Identification of the *HLXB9* gene mutation can confirm the diagnosis of Currarino syndrome but cannot predict the severity of the disorder because of broad phenotypic variability in the expression of Currarino syndrome and lack of genotype–phenotype correlation. Prenatal diagnosis of Currarino syndrome by ultrasound is possible in pregnancy with a positive family history. Friedmann et al [10] first described the prenatal diagnosis of Currarino triad by the sonographic findings of a 1 cm cystic presacral mass in a 25-week gestation fetus whose mother was known to have Currarino syndrome. Eliáš et al [11] reported the prenatal sonographic diagnosis of Currarino triad in a 21-week gestation fetus with a sigmoid kidney, a sacral bony defect, and low-lying medullary conus. Magnetic resonance imaging (MRI) at 32 gestational weeks revealed a rounded presacral, predominantly solid mass measuring about 1 cm and causing spinal cord tethering. The mother was simultaneously found to have Currarino triad by MRI. Crétolle et al [12] reported the prenatal diagnosis of Currarino syndrome in a 22-week gestation fetus with ventriculomegaly and spinal dysraphism due to a c.584delA, p.H195fsX28 heterozygous frameshift *HLXB9* mutation inherited from the mother. The mother's first pregnancy resulted in a child with sickle-shaped sacrum associated with a low-type anorectal malformation, a presacral teratoma, and an intraspinal lipoma in line with the low-lying medullary conus due to a maternally inherited pathogenic mutation in the *HLXB9* gene. The mother had a history of anal atresia with cutaneous fistula, neonatal intestinal occlusion, and a sickle-shaped sacrum. Because of the absence of genotype–phenotype correlation and an extremely high variability of phenotypes from typical triad to undetectable minor sacral abnormalities in the carriers of *HLXB9* mutations, preimplantation genetic diagnosis has been suggested as an important alternative for the at-risk pregnancy [13]. Verlinsky et al [13] reported the first preimplantation genetic diagnosis for the *HLXB9* mutation in an at-risk couple. The couple had a previous child with Currarino syndrome, imperforate anus, anterior meningocele, and a sickle-shaped sacrum. The husband had a mutation in the *HLXB9* gene and a history of anal stricture and a sacral defect. One of his two sisters had imperforate anus, anterior meningocele, rectovaginal fistula, and a sacral defect, and the other sister had anterior meningocele and no coccyx.

Sacral Defect with Anterior Meningocele (SDAM)

SDAM (OMIM 600145) is an autosomal dominant disorder. Fellous et al [14] reported a five-generation family with sacral agenesis and spina bifida, and suggested an autosomal dominant inheritance of the disease. Chatkupt et al [15] reported autosomal dominant SDAM in a five-generation family in which the family members had hemisacral defects with or without anterior meningocele. Gardner and Albright [16] reported hereditary anterior sacral meningocele and hemisacral defects in a mother and her son. Both SDAM and Currarino triad can be associated with the sacral defect and anterior meningocele. Female patients with SDAM may experience obstructive labor because of anterior meningocele. SDAM may be associated with mutations in the *VANGL1* gene (OMIM 610132) on 1p13. Kibar et al [17] suggested that mutations in the *VANGL1* gene are associated with NTDs in humans. Kibar et al [17] described a missense mutation in the *VANGL1* gene resulting in a substitution of valine with isoleucine or V239I in a 10-year-old Italian girl with caudal regression (type IV of sacral agenesis), lipomyeloschisis, anorectal malformations, hydromelia, and a tethered spinal cord. The girl's mother and brother carried the V239I mutation in the *VANGL1* gene. The mother showed no signs of NTDs, but the brother had a mild NTD with dermal sinus.

Jarcho-Levin Syndrome (Spondylocostal Dysostosis)

Jarcho-Levin syndrome or spondylocostal dysostosis is an autosomal recessive disorder. Spondylocostal dysostosis is characterized by a shortened trunk, an opisthotonus position of the head, a short neck, a barrel-shaped thorax, multiple wedge-shaped and block vertebrae, spina bifida, and rib anomalies. Spina bifida is present in 25% of patients [18]. Mutations in the genes that are important components of the Notch signaling pathway are responsible for the development of spondylocostal dysostosis. Spondylocostal dysostosis, autosomal recessive 1 (SCDO1; OMIM 277300) is caused by mutations in the *DLL3* gene (OMIM 602768) at 19q13; spondylocostal dysostosis, autosomal recessive 2 (SCDO2; OMIM 608681) is caused by mutations in the *MESP2* gene (OMIM 605195) at 15q26.1; and spondylocostal dysostosis, autosomal recessive 3 (SCDO3; OMIM 609813) is caused by mutations in the *LFNG* gene (OMIM 602576) at 7p22. NTDs can be associated with segmental costovertebral malformations [19–28]. Reyes et al [19] reported a case of Jarcho-Levin syndrome with diastematomyelia of the thoracolumbar spinal cord and suggested NTDs as a component of Jarcho-Levin syndrome. Giacoia and Say [20] reported a patient with Jarcho-Levin syndrome, spina bifida, and diastematomyelia, and concluded that Jarcho-Levin syndrome and NTDs are etiologically related. Rodriguez et al [21] reported an infant with Jarcho-Levin syndrome, thoracolumbar meningocele, imperforate anus, and perinatal death. Duru et al [22] reported two patients with Jarcho-Levin syndrome and NTDs, one of whom with lumbosacral lipomyelomeningocele and the other with thoracolumbar myelomeningocele. Etus et al [23] reported a patient with Jarcho-Levin syndrome, type I split cord malformation, and an accompanying spinal lipoma. Kauffmann et al [24] reported the first-trimester prenatal diagnosis of Jarcho-Levin syndrome in a fetus with sonographic findings of a shortened spine, vertebral disorganization, increased nuchal translucency thickness, spina bifida, and renal calyces dilation at 13 gestational weeks. Nadkarni et al [25] reported two patients with segmental costovertebral malformation and lumbosacral lipomyelomeningocele. Yi et al [26] reported a case of Jarcho-Levin syndrome with intrathoracic myelomeningocele. Dane et al [27] reported the first-trimester prenatal diagnosis of Jarcho-Levin syndrome in a fetus with sonographic findings of a shortened spine, kyphoscoliosis, and spina bifida at 13 gestational weeks. Dane et al [28] reported four cases of Jarcho-Levin syndrome with NTDs as the prominent prenatal diagnosis. Their first case had sonographic findings of a vertebral disorganization, lumbosacral spina bifida, bilateral talipes, and fixed extension of the lower limbs at 24 gestational weeks. The second case had sonographic findings of a vertebral disorganization, a shortened spine, thoracolumbar spina bifida, hydrocephalus, skeletal kyphoscoliosis, and an asymmetric short thorax at 24 gestational weeks. The third case had sonographic findings of a vertebral disorganization, thoracolumbar spina bifida, hydrocephalus, an asymmetric thorax, a short truck, talipes, extension of the lower limbs, and a prominent occiput at 22 gestational weeks. The fourth case had sonographic findings of lumbosacral spina bifida, severe kyphosis, talipes, and fixed extension of the lower limbs at 20 gestational weeks. Prenatal diagnosis of vertebral deformities or spina bifida should raise a suspicion of Jarcho-Levin syndrome [29,30]. Fetuses with Jarcho-Levin syndrome may present with increased nuchal translucency thickness on prenatal ultrasound in the first trimester [31–33].

Lateral Meningocele Syndrome (LMS)

LMS (OMIM 130720) or Lehman syndrome is characterized by multiple lateral meningoceles in the absence of neurofibromatosis and Marfan syndrome. Other clinical features of LMS include scoliosis, kyphosis, joint hypermobility, pectus deformities, umbilical/inguinal hernias, wormian bones, loose skin, and craniofacial abnormalities such as ocular hypertelorism, downslanting palpebral fissures, ptosis, low-set posteriorly rotated ears, abnormal palate, molar hypoplasia and micrognathia, suggesting an underlying connective tissue dysplasia [34–38]. Lateral meningoceles are protrusions of the arachnoid and the dura matter through inter- or intravertebral foramina, and can present as widening of the neural canal, thinning of the bony cortex of the vertebral bodies and pedicles, dilation of the neural foramina, and protrusion of dura outside the neural canal [37]. LMS was first described in a 14-year-old girl with generalized osteosclerosis, distinctive craniofacial features, and multiple thoracic and lateral meningoceles [34]. The mother was asymptomatic but had similar craniofacial features. Gripp et al [37] suggested the term "lateral meningocele syndrome". Chen et al [38] suggested that LMS is an autosomal dominant disorder, although X-linked inheritance cannot be excluded because of the absence of reported male-to-male transmission.

Neurofibromatosis Type I (NF1)

NF1 (OMIM 162200), characterized by café-au-lait spots and fibromatous tumors of the skin, is caused by

mutations in the neurofibromin gene (*NF1*) on chromosome 17q11.2. NF1 is an autosomal dominant disorder. Meningoceles can be associated with NF1 especially in adults because of body defects of vertebral scalloping, enlarged foramina, and deformed pedicles. NF1 is seen in 63% of thoracic lateral meningoceles [39]. Nakasu et al [40] first reported computed tomography (CT) and MRI findings of a thoracic meningocele in a 53-year-old female with NF1. Bensaid et al [41] reported dural ectasia, a form of mild meningocele, and bilateral symmetrical pedicular clefts in a 30-year-old female and a 32-year-old female with NF1. Freund and Timon [42] reported a 54-year-old female with NF1 and a cervical meningocele presenting as a neck mass. Rainov et al [43] described a 33-year-old female and a 53-year-old male with NF1, ventrolateral thoracic and lumbar meningoceles, neurologic signs, and severe pain. Miyata et al [44] reported resection of a right lumbar lateral meningocele in a 29-year-old female with NF1. Yoshioka et al [45] reported intracranial vascular malformation and a meningocele in a 21-year-old male with NF1. Kapadia et al [46] reported diffuse neurofibroma of the orbit and temporal meningocele in an 8-year-old girl with NF1. de Vries et al [47] reported successful surgical repair of progressive exophthalmos caused by a protruding meningocele in a 43-year-old female with NF1. Kurimoto et al [48] reported surgical extirpations of a suboccipital meningocele presenting as a huge retropharyngeal mass in a 73-year-old female with NF1. Chapmann et al [49] reported an unusual pterygopalatine meningocele in an 8-year-old boy associated with NF1. Ogose et al [50] reported an intrathoracic meningocele in a 42-year-old female with NF1. Mizuno et al [51] reported a giant intrathoracic meningocele and hydrothorax in a 67-year-old female with NF1. Ebara et al [52] reported severe kyphoscoliosis and an intrathoracic meningocele in a 59-year-old male with NF1. Reis et al [53] reported epithelioid hemangioendothelioma and multiple thoracolumbar lateral meningoceles in a 31-year-old female with NF1.

Marfan Syndrome

Marfan syndrome (OMIM 154700) is a connective tissue disorder with classical manifestations of aortic, skeletal and ocular abnormalities. Marfan syndrome is characterized by arachnodactyly with hyperextensibility, pectus carinatum, pectus excavatum, scoliosis, spondylolisthesis, pes planus, protrusio acetabuli, lens subluxation, and aortic dilation. Marfan syndrome is caused by mutations in the fibrillin-1 gene (OMIM 134797) on chromosome 15q21.1 and has an autosomal dominant inheritance pattern with wide variability in expression. Dural ectasia is a common feature of Marfan syndrome. Pyeritz et al [54] reported that 63% (36/57) of the patients with Marfan syndrome had widening of the lumbosacral spinal canal and dural ectasia. Using CT, Villeirs et al [55] assessed the widening of the spinal canal and dural ectasia in Marfan syndrome. Using MRI, Fattori et al [56] identified that 92% (76/83) of the patients with Marfan syndrome had dural ectasia. Dural ectasia is a ballooning or widening of the dural sac and is often associated with herniation of the nerve root sleeves out of the associated foramina [57]. Dural ectasia may be associated with NF1, Marfan syndrome, Ehlers-Danlos syndrome, and ankylosing spondylitis. Ahn et al [57] suggested the criteria of dural ectasia on MRI and CT images in adult Marfan patients. The major criteria include: (1) width of dural sac below L5 > width below L4, and (2) anterior sacral meningocele. The minor criteria include: (1) L5 nerve root sleeve diameter > 6.5 mm, and (2) S1 scalloping > 3.5. Dural ectasia exists if one major or two minor criteria are present. Strand and Eisenberg [58] reported anterior sacral meningocele in association with Marfan syndrome in a 10-year-old boy. Harkens and el-Khoury [59] reported intrasacral meningocele in a 54-year-old male with Marfan syndrome. Raftopoulos et al [60] described a huge bilobed complex sacral meningocele cured endoscopically in a 33-year-old female with Marfan syndrome. Schneider et al [61] reported anterior sacral meningocele presenting as a pelvic/abdominal mass in a 25-year-old female with Marfan syndrome. Voyvodic et al [62] reported two Marfan females with anterior sacral meningoceles presenting as non-gynecologic pelvic masses. The presence of dural ectasia is associated with back pain in more than 50% of patients with Marfan syndrome; however, dural ectasia was noted to exist in 41% of patients with Marfan syndrome without back pain [63]. Rigante and Segni [64] reported anterior sacral meningocele in an 18-year-old male with Marfan syndrome. Nallamshetty et al [65] reported a significantly large anterior sacral meningocele in a 52-year-old female without associated symptoms.

Hyperthermia

In humans, an oral temperature of 37°C or a deep body (core) temperature of 38°C is considered normal [66]. A 2°C elevation of maternal temperature to 39°C in oral temperature or to 40°C in core temperature is regarded as the threshold of damage [67]. In humans, a body temperature above the upper limit of the normal range has been associated with NTDs [68–83]. In a

comparative study involving 23,491 women of hyperthermic exposure limited to hot tub, sauna, fever or electric blanket in New England, Milunsky et al [78] found that exposure to heat in the form of hot tub, sauna or fever in the first trimester of pregnancy was associated with an increased risk for NTDs. The relative risks (RRs) were 2.8 (95% confidence interval, CI, 1.2–6.5) for hot tub use, 1.8 (95% CI, 0.4–7.9) for sauna, 1.8 (95% CI, 0.8–4.1) for fever, and 1.2 (95% CI, 0.5–2.6) for electric blanket; and when only hot tub use, sauna and fever were considered, the RR for NTDs increased from 1.9 (95% CI, 0.9–3.7) after one type of heat exposure to 6.2 (95% CI, 2.2–17.2) after two types of exposure [78]. In a comparative study involving 538 NTD cases and 538 non-malformed controls in California, Shaw et al [81] found that a maternal fever or febrile illness episode in the first trimester was associated with an increased risk for having an NTD-affected pregnancy with an odds ratio (OR) of 1.91 (90% CI, 1.35–2.72) for fever and an OR of 2.02 (95% CI, 1.20–3.43) for febrile illness. In a comparative study involving 175 NTD cases and 221 controls in a Texas-Mexico border population, Suarez et al [83] found that maternal hyperthermia was associated with an increased risk of NTDs. The RR was 3.6 (95% CI, 1.1–15.9) for first-trimester maternal exposures to heat devices such as hot tubs, saunas or electric blankets, and small insignificant effects were observed for cooking in a hot kitchen (OR, 1.6; 95% CI, 1.0–2.6) and working or exercising in the sun (OR, 1.4; 95% CI, 0.9–2.2). In a meta-analysis of 15 studies from 1966 to 2003 that included 1,719 NTD cases and 37,898 non-cases, Moretti et al [84] found that the overall OR for NTDs associated with maternal hyperthermia was 1.92 (95% CI, 1.61–2.29), and concluded that maternal hyperthermia in early pregnancy is associated with an increased risk for NTDs and may be a human teratogen. The Centers for Disease Control and Prevention [85] suggested that women of reproductive age should take 400 μg of supplemental folic acid daily to reduce the risk of NTDs. Medveczky et al [86] concluded that maternal fever is a possible cause of NTDs, and maternal fever during pregnancy should be treated with antipyretics. Chambers [87] suggested that women of reproductive age should also be aware of the possible variability in hot tub or spa temperature reading, and be able to accurately monitor maximum water temperature in the hot tub or spa to reduce the risk of NTDs. Harvey et al [88] suggested limits for the use of hot tub and sauna by pregnant women to less than 15 min in 39°C water and to less than 10 min in 40°C water. The recommended time should be reduced if there exist other risk factors such as poor health, fever, exercise or any source of hyperthermia [87]. Susceptibility to hyperthermia-induced NTDs appears to be associated with an embryonic effect through elevation of the maternal core temperature [89], a dose-response of temperature and duration of exposure [90], and a genetic basis [91,92]. In a study of the effect of hyperthermia on rat embryos in culture by completely removing the embryo from maternal influence and exposing rat embryonic explants to mild hyperthermic insult during the onset of neural tube closure, Cockroft and New [89] found that nearly one-half of the exposed rat embryos were microcephalic. In a study of the parameters determining hyperthermia-induced head defects in the rat, Germain et al [90] found a dose-response manner of temperature and duration of exposure in the induction of NTDs in the experimental animals. Finnell et al [91,92] hypothesized that subtle genetic changes can result in NTDs by the findings of strain-dependent differences in susceptibility to teratogenic insults and altered patterns of gene expression observed within the neuroepithelium of the affected embryos. Lundberg et al [93] reported the first genetic dissection of maternal hyperthermia-induced NTD in mice and demonstrated that a single fetal genetic locus and a maternal effect can cause the strain differences in the susceptibility to hyperthermia-induced exencephaly. Yang et al [94] recently identified the differentially expressed genes that participate in the pathologic course of hyperthermia-induced NTDs in golden hamsters using suppression subtractive hybridization.

Conclusion

This article provides a comprehensive review of syndromes, disorders, and maternal risk factors associated with NTDs, such as Currarino syndrome, SDAM, Jarcho-Levin syndrome (spondylocostal dysostosis), LMS, NF1, Marfan syndrome and hyperthermia. NTDs associated with syndromes, disorders, and maternal risk factors are a rare but important cause of NTDs. The recurrence risk and the preventive effect of maternal folic acid intake in NTDs associated with syndromes, disorders, and maternal risk factors may be different from those of non-syndromic multifactorial NTDs. Perinatal identification of NTDs should alert one to the syndromes, disorders, and maternal risk factors associated with NTDs, and prompt a thorough etiologic investigation and genetic counseling.

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